

### **REMARKS**

Claims 27-32 are pending in this application. No claim amendments are presented at this time. A telephone interview was held on July 24, 2008 in connection with this application. Applicants note with appreciation that the previous rejection under 35 U.S.C. §103(a) for obviousness has been withdrawn; however, a new obviousness rejection has been issued. Applicants respectfully request reconsideration of this application in view of the remarks presented below and allowance of the pending claims to issue.

#### **Interview Summary.**

Applicants wish to express their appreciation to the Examiner for the time and courtesy extended during the telephonic interview on July 24, 2008 with Applicants' representative, Karen Magri. During the course of the interview, the Chanas et al. reference was discussed. The Examiner indicated that his preliminary thoughts were that the Applicants' arguments appeared persuasive, but that he would need to reconsider the arguments and the Chanas et al. reference once he received this written response.

#### **Claim Rejections under 35 U.S.C. § 103(a).**

Claims 27-32 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over WO 95/32733 (Johnston et al.) in view of Chanas et al. (*J. Gen. Virol.* 57: 38 (1982)). This rejection is respectfully traversed below.

The Office Action states that Johnston et al. teaches a method of administering a VEE virus that expresses a heterologous immunogen as a vaccine, but concedes that "Johnston et al. do not teach to administer an antibody that specifically binds to the E1 glycoprotein of VEE along with the VEE." The Office Action states that Chanas et al. teach that monoclonal antibodies specific for the E1 glycoprotein of Sindbis virus can at particular concentrations enhance infectivity for macrophage-like cells, and further "Chanas demonstrates this effect by administering a sindbis virus (which is an alphavirus) with the E1 glycoprotein-specific antibodies to a mouse." Finally, the Office Action concludes that the combination of Johnston et al. and Chanas et al. renders the present invention obvious. As discussed in more detail below, Applicants respectfully disagree with this rejection.

Chanas et al. is concerned with dissecting the roles of the Sindbis virus surface glycoproteins, E1 and E2, in neutralization of infectivity, hemagglutination, and hemolysis (Chanas et al., page 37, Introduction, lines 3-9). Chanas et al. proposed to use monoclonal

antibodies to "define precisely the function of the surface proteins of the virus" (Chanas et al., page 37, Introduction, lines 17-18). Chanas et al. reported that monoclonal antibodies specific for Sindbis E1 glycoprotein "can neutralize infectivity, enhance infectivity for macrophage-like cells and separately inhibit haemagglutination and haemolysis." (Chanas et al., page 37, Introduction, last paragraph).

Chanas et al. did observe enhancement of infectivity by the wild-type Sindbis clone AR339 (page 37, Methods, first paragraph) in cultured P388D<sub>1</sub> macrophage-like cells, but not in Vero cells, with monoclonal antibodies against the Sindbis E1 glycoprotein or hyperimmune serum (Chanas et al., Figures 3-4 and page 42). However, contrary to the assertions in the outstanding rejection, Chanas et al. did not report antibody-dependent enhancement of Sindbis infectivity in mice (or in any other whole animal model).

In fact, Chanas et al. teach that administration of wild-type Sindbis virus AR339 and one of the anti-E1 antibodies intracerebrally into newborn mice "gave almost complete protection against challenge with Sindbis virus." (Chanas et al., page 43, last sentence). In other words, Chanas et al. only observed neutralization of Sindbis virus infectivity *in vivo*; Chanas et al. provides no teachings whatsoever regarding antibody-dependent enhancement of virus infectivity *in vivo*. By "neutralization" it is meant that the antibody treatment inhibited virus infectivity. This is a fundamentally different effect than enhancing the ability of a virus or vector to infect cells.

Briefly, Chanas et al. divided newborn mice into treatment groups that received various doses of Sindbis virus and ascitic fluid (control) or monoclonal antibody 30.12 or 30.11 ascitic fluid, or hyperimmune serum by intracerebral inoculation. Following treatment, average survival time was measured. The results are shown in Table 4 of the Chanas et al. publication.

As expected, the control animals died quickly (average survival time of 1.0, 1.5 and 1.8 days for the three virus dosage groups; Table 4, column 2); Sindbis virus is known to be lethal when administered by intracerebral inoculation into newborn mouse brain. Prior co-incubation and administration of Sindbis virus with monoclonal antibody 30.11 resulted in a substantial prolongation of average survival time of the mice (*i.e.*, 14.8, 17.6 and 17.2 days for the three virus dosage groups; Table 4, column 4). Neutralization was also observed with hyperimmune serum, and monoclonal antibody 30.12 gave a "slight but consistent" prolongation in average mouse survival (Chanas et al. page 43, last line and page 44, lines 1-2; Table 4, columns 3 and 5).

These results demonstrate that the anti-E1 antibodies and hyperimmune serum neutralized Sindbis virus infectivity in newborn mouse brain, thereby reducing the lethal effects of the virus. Thus, if anything, Chanas et al. teaches away from the present invention and certainly does not render obvious the claimed methods of administering a VEE vector comprising a heterologous nucleotide sequence and an antibody that specifically binds the E1 and/or E2 glycoprotein of VEE to a subject.

In sum, Applicants respectfully submit that the subject matter of claims 27-32 is novel and nonobvious over Johnston et al. in view of Chanas et al. and respectfully request that the rejection under 35 U.S.C. 103(a) over the combination of these references be withdrawn.

**Conclusion.**

Having addressed all of the issues raised by the Examiner in the pending Office Action, Applicants respectfully request the withdrawal of the pending rejections and allowance of the pending claims to issue. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of this application to allowance.

A petition for a two-month extension of time is enclosed herewith. The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



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Katie Wu